encoding firefly luciferase, a gene encoding bacterial luciferase, [and]or a gene encoding alkaline phosphatase.

68. (**Amended**) The method of claim 63, wherein the transcriptional control region includes at least one regulatory element selected from [the group consisting of] transcriptional regulatory elements of a patched gene, [a] transcriptional regulatory elements of a gli gene, [and a]or transcriptional regulatory elements of a PTHrP gene.

74. (**Amended**) The method of claim 61 or 62, further comprising preparing a formulation including an agent which affects patched-dependent signal transduction [identified as useful for ameliorating an effect of loss of function of a patched gene] and a pharmaceutically acceptable excipient.

76. (**Amended**) The method of claim 63, further comprising preparing a formulation including an agent which affects patched-dependent signal transduction [for modulating proliferation] and a pharmaceutically acceptable excipient.

REMARKS

Claims 61-77 constitute the pending claims in the present application. Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

1. Applicants note with appreciation that the rejection of claims 62-73 under 35 U.S.C. 112, first paragraph have been withdrawn.

2. Claims 62 and 72-75 are rejected under 35 U.S.C. 112, first paragraph as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application

was filed, had possession of the claimed invention. Applicants traverse this rejection to the extent it is maintained over the amended claims.

Applicants maintain that one of skill in the art would readily recognize that mutations at other points in the patched signaling cascade would also cause a patched loss-of-function phenotype. Additionally, Applicants cite the following passages from the specification to demonstrate that Applicants were in possession of this matter at the time of filing of the application. "Certain human cancers, e.g., basal cell carcinoma, transitional cell carcinoma of the bladder, meningiomas, medulloblastomas, etc., can be characterized by ptc loss-of-function, such as that resulting from oncogenic mutations at the ptc locus, or other loss-of-function mutations which decrease ptc activity in a cell." (page 5, lines 33-36). "[T]he drug screening assay is a cell-based assay which detects the ability of a compound to alter patched-dependent gene transcription. By selecting transcriptional regulatory sequences from genes whose expression is regulated by patched signal transduction, e.g., from patched, Gli, hedgehog or PTHrP genes, e.g., regulatory sequences that are responsible for the up- or down regulation of these genes in response to patched signaling, and operatively linking such promoters to a reporter gene, one can derive a transcription based assay which is sensitive to the ability of a specific test compound to modify patched signaling pathways." (page 20, line 30-37). "[T]wo other proteins work together with Hh to activate target genes: the ser/thr kinase fused and the zinc finger protein encoded by cubitus interruptus. Negative regulators working together with ptc to repress targets are protein kinase A and costal 2. Thus, mutations that inactivate human versions of protein kinase A or costal 2, or that cause excessive activity of human hh, gli, or a fused homolog, may modify the BCNS phenotype and be important in tumorigenesis." (page 33, lines 11-16). "Reporter gene based assays of this invention measure the end stage of the above described cascade of events, e.g., transcriptional modulation. Accordingly, in practicing one embodiment of the assay, a reporter gene construct is inserted into the reagent cell in order to generate a detection signal dependent on ptc signaling." (page 21, lines 3-6).

Accordingly, Applicants maintain that the written description requirement has been met, and that Applicants were in possession of the full scope of the claimed invention including loss-of-patched function resulting from mutations at other points in the signaling pathway. Reconsideration and withdrawal of the rejection is respectfully requested.

3. Claims 61-77 are rejected under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, particularly for failing to enable for methods of identifying agents which are useful for treating an animal having a disorder characterized by loss of function of a *patched* gene. Applicants traverse this rejection to the extend that it is maintained over the amended claims.

Applicants point out that in accordance with MPEP 2164.02, "[a]n example may be either working or prophetic. A prophetic example describes an embodiment of the invention based on predicted results rather than work actually conducted or results actually achieved." Applicants have provided an extensive discussion of patched and hedgehog signaling, including the role of patched as a tumor suppressor gene and the link between mutations in patched and proliferative disorders in both mouse models and human patients (see, for example, page 36, line 29-page 37, line18: page 41, table 2). Given the role of patched and hedgehog signaling in a wide range of proliferative disorders, Applicants have disclosed prophetic examples which include the use of the subject methods to identify agents which affect cell proliferation. The standard for enablement is not whether Applicants have reduced every embodiment encompassed by the claims to practice, but whether one of skill in the art could practice the claimed invention without undue experimentation in light of the disclosure and the state of the art. Certainly, given the well established role of patched as a tumor suppressor, and the involvement of hedgehog signaling in a wide range of proliferative disorders, one of skill in the art would be able to practice the claimed methods in light of the disclosure, and would have a reasonable expectation of success of identifying agents which affect cell proliferation.

The Examiner is reminded that in accordance with MPEP 2164.06, the fact that the amount of experimentation required is extensive or time consuming does not make such experimentation undue. "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). "An

extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance." *In re Colianni*, 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977).

The claims are additionally rejected for allegedly failing to enable for in vivo methods of treatment. Once again, Applicants have presented a prophetic example of an embodiment of the invention, and the standard for evaluating this embodiment is whether one of skill could determine whether the embodiment is operative or inoperative. Applicants have provided an animal model which can be readily used by one of skill in the art to hone in on the identified agents likely to have therapeutic potential before initiating further in vivo human experiments. For example, Applicants have provided patched "knock-out" mice (homozygous patched loss-of-function mice, pages 34-46), as well as patched heterozygous mice which have a phenotype which includes medulloblastomas and skeletal defects (page 36-38). One of skill can readily use cells and tissue from these animals to test the lead compounds identified by the methods of the present invention.

PCT application WO01/26644 (enclosed herewith as Exhibit 1) demonstrates that, following the teachings of the present application, one of skill could identify compounds that affect patched dependent signal transduction, and that such compounds can be further tested in animal models to demonstrate their efficacy in reversing a loss-of-patched function phenotype. For example, in WO01/26644, test compound D was tested in the gli-Luc cell based in vitro system for an effect on patched signal transduction. Compound D was then tested in an animal model using skin punches from wildtype or patched null mice. These studies demonstrate that compound D has efficacy in reversing the BCC phenotype in skin from patched null mice. Accordingly, Applicants contend that this study demonstrates that the disclosure provides enablement of the full scope of the invention. Given the disclosed methods, one of skill in the art would have been able to identify a compound which affects patched signal transduction, and use that compound to affect cellular proliferation/and reverse the patched loss-of-function phenotype in an animal by following the teachings of the specification, in light of the level of skill in the art, without undue experimentation.

In accordance with MPEP 2164.02, "if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless

the examiner has evidence that the model does not correlate." Applicants further point out that "a rigorous or an invariable exact correlation is not required." As stated in Cross v. Iizuka, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985). "[B]ased upon the relevant evidence as a whole, there is a reasonable correlation between the disclosed in vitro utility and an in vivo activity, and therefore a rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence."

The Office Action cites the unpredictability in predicting the ultimate efficacy of drugs for the treatment of diseases. However, in accordance with MPEP 2107.02 (V), "it is improper for Office personnel to request evidence of safety in the treatment of humans, or regarding the degree of effectiveness." Although the process of ultimately identifying drugs which can be brought *to market* is a long, arduous, and perhaps unpredictable one, evaluating drugs on this basis is the responsibility of the FDA. "The office must confine its review of patent applications to the statutory requirements of the patent law. Other agencies of the government have been assigned the responsibility of ensuring conformance to standards established by statute for the advertisement, use, sale or distribution of drugs." (MPEP 2107.02 (V)). Whether an agent identified by the methods of this invention is ultimately suitable as a therapeutic *product* is not the standard for the enablement of the full scope of these claims.

Applicants maintain that the specification, in light of the level of skill in the art, enables one of skill to practice the claimed invention without undue experimentation. The specification provides extensive teachings that the patched tumor suppressor and hedgehog signaling are involved in a range of proliferative disorders, and thus one of skill in the art would have a reasonable expectation of success of using the subject methods to identify agents which affect cellular proliferation. The standard for the enablement of the scope of the claims is not whether Applicants have reduced to practice every embodiment of the claimed invention, but whether Applicants have provided sufficient guidance such that one of skill in the art can reduce the embodiment to practice using the disclosure and the level of skill in the art. Applicants contend that the level of skill in the art is high, and that even if the amount of experimentation necessary to practice the invention may be extensive, such experimentation is routine. Applicants contention that the claims are enabled throughout their scope is further supported by Exhibit 1 which demonstrates that one of skill **can** use the disclosure to identify lead compounds which

can be further tested in in vitro and animal models for efficacy in affecting proliferation. Furthermore, in accordance with the MPEP, Applicants need not demonstrate that compounds identified using the claimed methods will ultimately gain FDA approval. Accordingly, Applicants have satisfied the standards for the enablement of the claimed subject matter. Reconsideration and withdrawal of this rejection is requested.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945.**

Respectfully Submitted,

Date: December 13, 2001

Matthew D. Vincent
Reg. No. 36,709

Customer No: 28120
Docketing Specialist
Ropes & Gray
One International Place
Boston, MA 02110